

In the claims:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

1-37. Cancelled.

38. (currently amended) ~~a-A~~ method for modifying glucose metabolism in a glucose intolerant animal, comprising administering to the animal, in a single daily oral dosage, a composition including one or more protease inhibitors which inhibit DPIV-mediated proteolysis with a  $K_i$  ~~in the nanomolar or less range of less than about 10 nM.~~

39. (currently amended) A method for modifying glucose metabolism in a glucose intolerant animal, comprising administering to the animal, in a single daily oral dosage, a composition including one or more protease inhibitors which inhibit the proteolysis of glucagon-like peptide 1 (GLP-1) with a  $K_i$  of less than about 10 nM. ~~in the nanomolar or less range.~~

40. (currently amended) A method for modifying metabolism of a peptide hormone in a glucose intolerant animal, comprising administering to the animal a composition, in a single daily oral dosage, including one or more inhibitors of dipeptidylpeptidase IV (DPIV), wherein the inhibitor inhibits DPIV with a  $K_i$  of less than about 10 nM. ~~in the nanomolar or less range~~, in an amount sufficient to increase the plasma half-life of the peptide hormone, which peptide hormone is selected from glucagon-like peptide 2 (GLP-2), growth hormone-releasing factor (GHRF), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), pituitary adenylate cyclase activating peptide (PACAP), gastric inhibitory peptide (GIP), helodermin, Peptide YY and neuropeptide Y.

41. (original) A method for modifying glucose metabolism of a glucose intolerant animal, comprising administering to the animal a composition including a boronyl

peptidomimetic inhibitor of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

42. (original) The method of claim 41 wherein, the glucose intolerance in the animal is a result of a deletion or disruption of the gene encoding for a glucagon type peptide 1 (GLP-1) receptor.

43. (Cancelled)

44, 45. (Cancelled)

46. (original) The method of claim 38, 39, 40 or 41, wherein administering the inhibitor reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia.

47. (original) The method of claim 38, 39, 40 or 41, wherein the inhibitor has an EC<sub>50</sub> for modification of glucose metabolism which is at least one order of magnitude less than its EC<sub>50</sub> for immunosuppression.

48. (original) The method of claim 38, 39, 40 or 41, wherein the inhibitor has an EC<sub>50</sub> for inhibition of glucose tolerance in the nanomolar or less range.

49. (original) The method of claim 38, 39, 40 or 41, wherein the inhibitor has an EC<sub>50</sub> for immunosuppression in the  $\mu$ M or greater range.

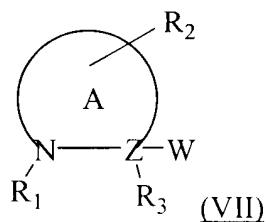
50. (original) The method of any of claim 38, 39, 40 or 41, wherein the inhibitor has a K<sub>i</sub> for DPIV inhibition of 0.5 nM or less.

51. (original) The method of claim 38, 39, or 40, wherein the inhibitor is peptidomimetic of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

52. (original) The method of claim 38, 39, 40 or 41, wherein the inhibitor has a molecular weight less than 7500 amu.

53. (original) The method of claim 38, 39, 40 or 41, wherein the inhibitor is administered orally.

54. (currently amended) ~~the~~ The method of claim 38, 39, 40 or 41, wherein the inhibitor is represented by the general Formula VII:

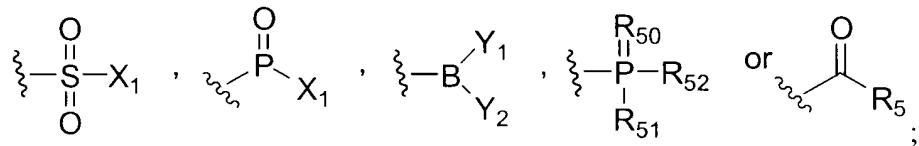


wherein,

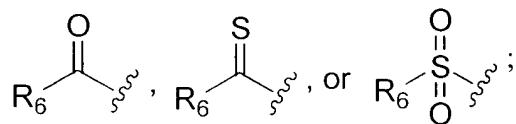
A represents a 4-8 membered heterocycle including a N and a C $\alpha$  carbon;

Z represents C or N;

W represents -CH=NR<sub>5</sub>,



R<sub>1</sub> represents a C-terminally linked amino acid residue or a amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group,



R<sub>2</sub> is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-OH, -(CH<sub>2</sub>)<sub>m</sub>-

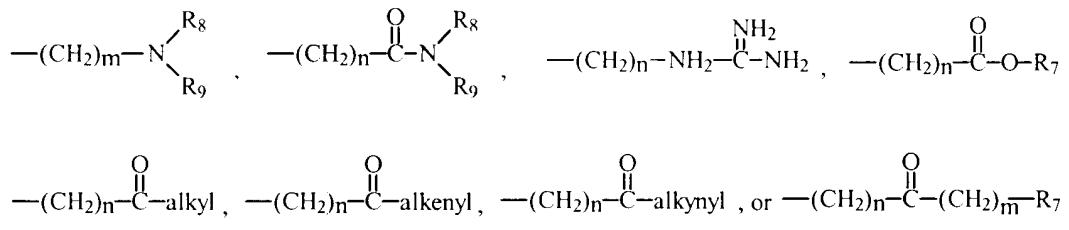
O-lower alkyl,  $-(CH_2)_m$ -O-lower alkenyl,  $-(CH_2)_n$ -O- $(CH_2)_m$ -R<sub>7</sub>,  $-(CH_2)_m$ -SH,  $-(CH_2)_m$ -S-lower alkyl,  $-(CH_2)_m$ -S-lower alkenyl, or  $-(CH_2)_n$ -S- $(CH_2)_m$ -R<sub>7</sub>;

if Z is N, R<sub>3</sub> represents a hydrogen;

if Z is C, R<sub>3</sub> represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonamido,  $-(CH_2)_m$ -R<sub>7</sub>,  $-(CH_2)_m$ -OH,  $-(CH_2)_m$ -O-lower alkyl,  $-(CH_2)_m$ -O-lower alkenyl,  $-(CH_2)_n$ -O- $(CH_2)_m$ -R<sub>7</sub>,  $-(CH_2)_m$ -SH,  $-(CH_2)_m$ -S-lower alkyl,  $-(CH_2)_m$ -S-lower alkenyl, or  $-(CH_2)_n$ -S- $(CH_2)_m$ -R<sub>7</sub>;

R<sub>5</sub> represents a hydrogen, an alkyl, an alkenyl, an alkynyl,  $-C(X_1)(X_2)X_3$ ,  $-(CH_2)_m$ -R<sub>7</sub>,  $-(CH_2)_n$ -OH,  $-(CH_2)_n$ -O-alkyl,  $-(CH_2)_n$ -O-alkenyl,  $-(CH_2)_n$ -O-alkynyl,  $-(CH_2)_n$ -O- $(CH_2)_m$ -R<sub>7</sub>,  $-(CH_2)_n$ -SH,  $-(CH_2)_n$ -S-alkyl,  $-(CH_2)_n$ -S-alkenyl,  $-(CH_2)_n$ -S-alkynyl,  $-(CH_2)_n$ -S- $(CH_2)_m$ -R<sub>7</sub>,  $-C(O)C(O)NH_2$ , or  $-C(O)C(O)OR'$ ;

R<sub>6</sub> represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl,  $-(CH_2)_m$ -R<sub>7</sub>,  $-(CH_2)_m$ -OH,  $-(CH_2)_m$ -O-alkyl,  $-(CH_2)_m$ -O-alkenyl,  $-(CH_2)_m$ -O-alkynyl,  $-(CH_2)_m$ -O- $(CH_2)_m$ -R<sub>7</sub>,  $-(CH_2)_m$ -SH,  $-(CH_2)_m$ -S-alkyl,  $-(CH_2)_m$ -S-alkenyl,  $-(CH_2)_m$ -S-alkynyl,  $-(CH_2)_m$ -S- $(CH_2)_m$ -R<sub>7</sub>,



R<sub>7</sub> represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R' represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R<sub>8</sub> and R<sub>9</sub> each independently represent hydrogen, alkyl, alkenyl, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>,

or R<sub>8</sub> and R<sub>9</sub> taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R<sub>50</sub> represents O or S;

R<sub>51</sub> represents N<sub>3</sub>, SH, NH<sub>2</sub>, NO<sub>2</sub> or OR'<sub>7</sub>;

R<sub>52</sub> represents hydrogen, a lower alkyl, an amine, OR'<sub>7</sub>, or a pharmaceutically acceptable salt, or R<sub>51</sub> and R<sub>52</sub> taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

Y<sub>1</sub> and Y<sub>2</sub> can independently or together be OH or an alkoxy, or taken together Y<sub>1</sub> and Y<sub>2</sub> are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

X<sub>1</sub> represents a halogen;

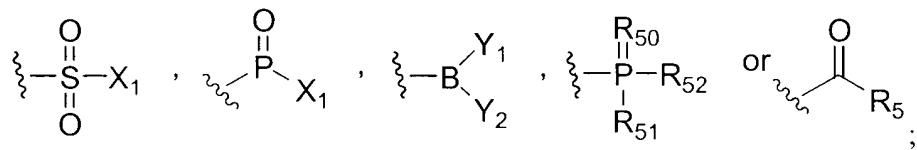
X<sub>2</sub> and X<sub>3</sub> each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

55. (original) The method of claim 54, wherein

W represents -CH=NR<sub>5</sub>,



R<sub>5</sub> represents a hydrogen, an alkyl, an alkenyl, an alkynyl, -C(X<sub>1</sub>)(X<sub>2</sub>)X<sub>3</sub>, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>n</sub>-OH, -(CH<sub>2</sub>)<sub>n</sub>-O-alkyl, -(CH<sub>2</sub>)<sub>n</sub>-O-alkenyl, -(CH<sub>2</sub>)<sub>n</sub>-O-alkynyl, -(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>n</sub>-SH, -(CH<sub>2</sub>)<sub>n</sub>-S-alkyl, -(CH<sub>2</sub>)<sub>n</sub>-S-alkenyl, -(CH<sub>2</sub>)<sub>n</sub>-S-alkynyl, -(CH<sub>2</sub>)<sub>n</sub>-S-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -C(O)C(O)NH<sub>2</sub>, or -C(O)C(O)OR'<sub>7</sub>;

R<sub>7</sub> represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'<sub>7</sub> represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

Y<sub>1</sub> and Y<sub>2</sub> can independently or together be hydroxyl, or taken together Y<sub>1</sub> and Y<sub>2</sub> are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

R<sub>50</sub> represents O or S;

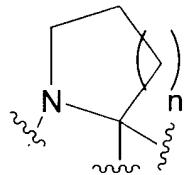
R<sub>51</sub> represents N<sub>3</sub>, SH, NH<sub>2</sub>, NO<sub>2</sub> or OR'<sub>7</sub>;

R<sub>52</sub> represents hydrogen, a lower alkyl, an amine, OR'<sub>7</sub>, or a pharmaceutically acceptable salt, or R<sub>51</sub> and R<sub>52</sub> taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X<sub>1</sub> represents a halogen; and

X<sub>2</sub> and X<sub>3</sub> each represent a hydrogen or a halogen.

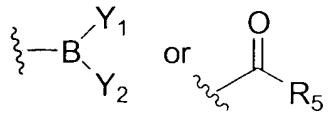
56. (original) The method of claim 54, wherein the ring A is represented by the formula



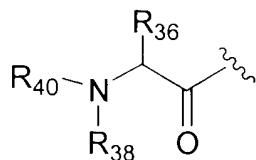
wherein,

n is an integer of 1 or 2.

57. (previously presented) The method of claim 54, wherein W represents



58. (original) The method of claim 54, wherein R<sub>1</sub> represents



R<sub>36</sub> represents a small hydrophobic group and R<sub>38</sub> is hydrogen, or, R<sub>36</sub> and R<sub>38</sub> together form a 4-7 membered heterocycle including the N and the C<sub>α</sub> carbon, as defined for A above; and

R<sub>40</sub> represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group.

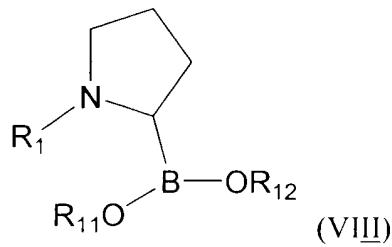
59. (original) The method of claim 54, wherein R<sub>2</sub> is absent, or represents a small hydrophobic group.

60. (original) The method of claim 54, wherein R<sub>3</sub> is a hydrogen, or a small hydrophobic group.

61. (original) The method of claim 54, wherein R<sub>5</sub> is a hydrogen, or a halogenated lower alkyl.

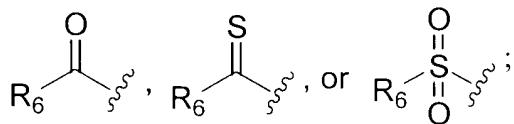
62. (original) The method of claim 54, wherein X<sub>1</sub> is a fluorine, and X<sub>2</sub> and X<sub>3</sub>, if halogens, are fluorine.

63. (original) The method of claim 54, wherein the inhibitor is represented by the general Formula (VIII):

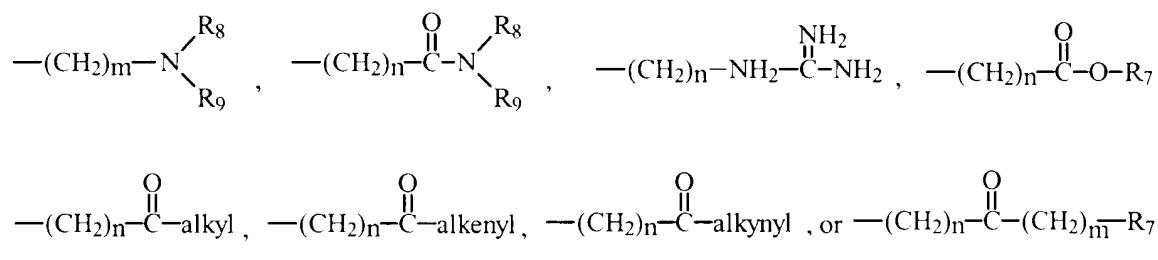


wherein,

R<sub>1</sub> represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog,



R<sub>6</sub> represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-OH, -(CH<sub>2</sub>)<sub>m</sub>-O-alkyl, -(CH<sub>2</sub>)<sub>m</sub>-O-alkenyl, -(CH<sub>2</sub>)<sub>m</sub>-O-alkynyl, -(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-SH, -(CH<sub>2</sub>)<sub>m</sub>-S-alkyl, -(CH<sub>2</sub>)<sub>m</sub>-S-alkenyl, -(CH<sub>2</sub>)<sub>m</sub>-S-alkynyl, -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>,



R<sub>7</sub> represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

R<sub>8</sub> and R<sub>9</sub> each independently represent hydrogen, alkyl, alkenyl, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>,

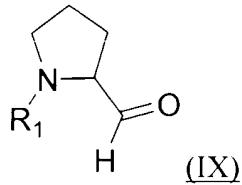
or R<sub>8</sub> and R<sub>9</sub> taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R<sub>11</sub> and R<sub>12</sub> each independently represent hydrogen, an alkyl, or a pharmaceutically acceptable salt, or R<sub>11</sub> and R<sub>12</sub> taken together with the O-B-O atoms to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

m is zero or an integer in the range of 1 to 8; and

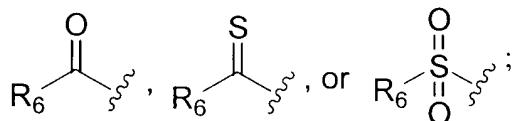
n is an integer in the range of 1 to 8.

64. (previously presented) The method of claim 54, wherein the inhibitor is represented by the general Formula IX:

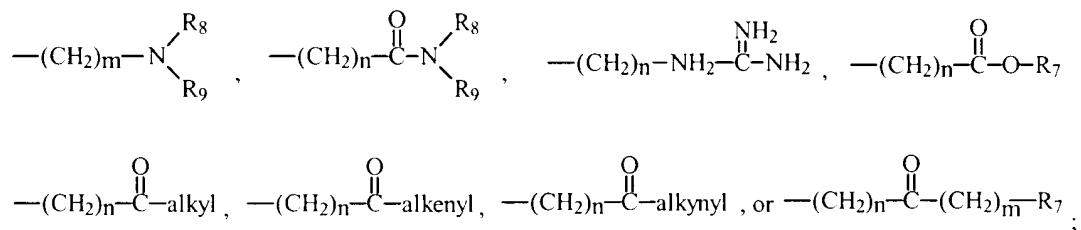


wherein

R<sub>1</sub> represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog,



R<sub>6</sub> represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-OH, -(CH<sub>2</sub>)<sub>m</sub>-O-alkyl, -(CH<sub>2</sub>)<sub>m</sub>-O-alkenyl, -(CH<sub>2</sub>)<sub>m</sub>-O-alkynyl, -(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-SH, -(CH<sub>2</sub>)<sub>m</sub>-S-alkyl, -(CH<sub>2</sub>)<sub>m</sub>-S-alkenyl, -(CH<sub>2</sub>)<sub>m</sub>-S-alkynyl, -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>,



R<sub>7</sub> represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

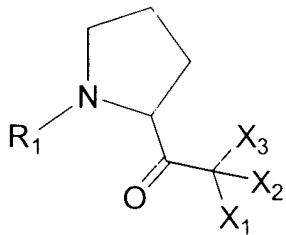
R<sub>8</sub> and R<sub>9</sub> each independently represent hydrogen, alkyl, alkenyl, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>,

or R<sub>8</sub> and R<sub>9</sub> taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

m is zero or an integer in the range of 1 to 8; and

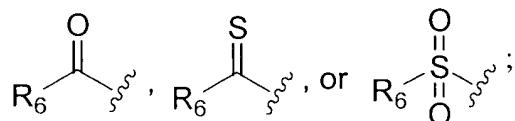
n is an integer in the range of 1 to 8.

65. (previously presented) The method of claim 54, wherein the inhibitor is represented by the general formula:

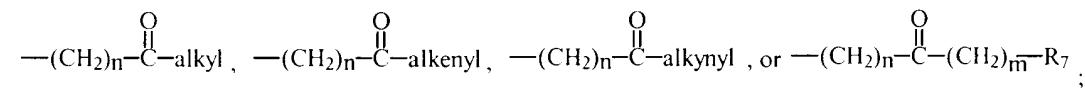
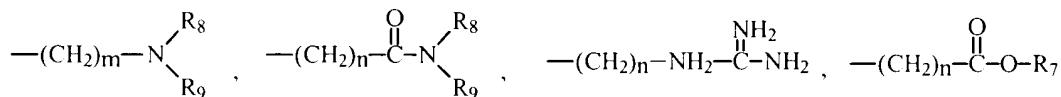


wherein,

$R_1$  represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide, or peptide analog,



$R_6$  represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl,  $-(CH_2)_m-$   $R_7$ ,  $-(CH_2)_m-OH$ ,  $-(CH_2)_m-O$ -alkyl,  $-(CH_2)_m-O$ -alkenyl,  $-(CH_2)_m-O$ -alkynyl,  $-(CH_2)_m-O-(CH_2)_m-R_7$ ,  $-(CH_2)_m-SH$ ,  $-(CH_2)_m-S$ -alkyl,  $-(CH_2)_m-S$ -alkenyl,  $-(CH_2)_m-S$ -alkynyl,  $-(CH_2)_m-S-(CH_2)_m-R_7$ ,



$R_7$  represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

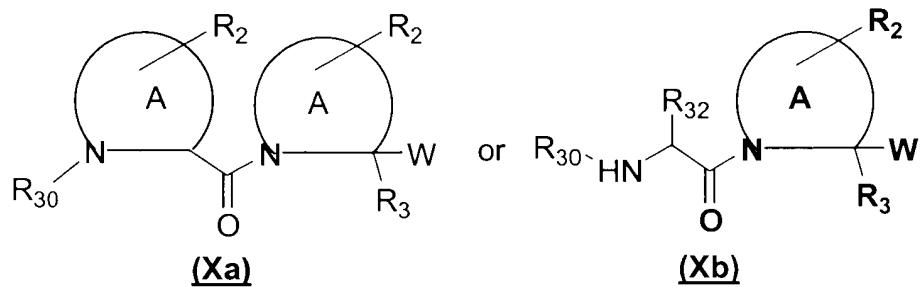
$R_8$  and  $R_9$  each independently represent hydrogen, alkyl, alkenyl,  $-(CH_2)_m-R_7$ ,  $-C(=O)$ -alkyl,  $-C(=O)$ -alkenyl,  $-C(=O)$ -alkynyl,  $-C(=O)-(CH_2)_m-R_7$ , or

$R_8$  and  $R_9$  taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

$X_1$ ,  $X_2$  and  $X_3$  each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and  
n is an integer in the range of 1 to 8.

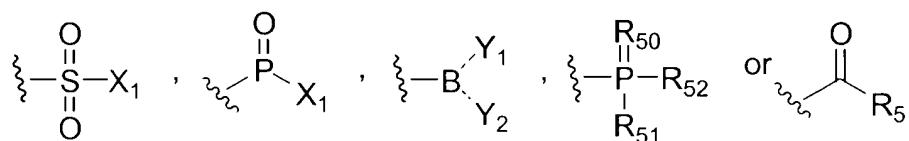
66. (currently amended) the method of claim 54, wherein the inhibitor is represented by the general Formula Xa or Xb:



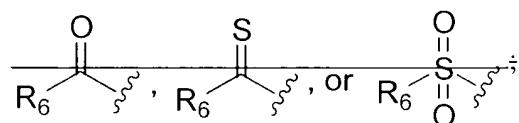
wherein,

A represents a 4-8 membered heterocycle including a N and a C $\alpha$  carbon;

W represents  $-\text{CN}$ ,  $-\text{CH}=\text{NR}_5$ ,



$R_4$  represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group,

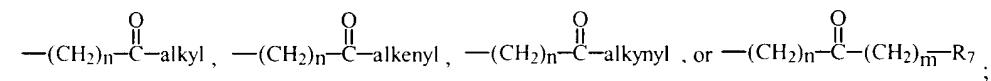
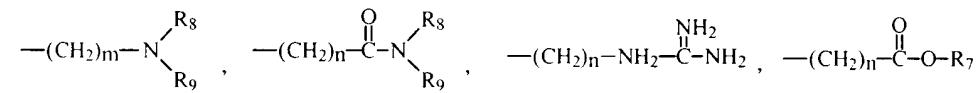


R<sub>2</sub> is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-OH, -(CH<sub>2</sub>)<sub>m</sub>-O-lower alkyl, -(CH<sub>2</sub>)<sub>m</sub>-O-lower alkenyl, -(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-SH, -(CH<sub>2</sub>)<sub>m</sub>-S-lower alkyl, -(CH<sub>2</sub>)<sub>m</sub>-S-lower alkenyl, or -(CH<sub>2</sub>)<sub>n</sub>-S-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>;

$R_3$  represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido,  $-(CH_2)_m-R_7$ ,  $-(CH_2)_m-OH$ ,  $-(CH_2)_m-O$ -lower alkyl,  $-(CH_2)_m-O$ -lower alkenyl,  $-(CH_2)_n-O-(CH_2)_m-R_7$ ,  $-(CH_2)_m-SH$ ,  $-(CH_2)_m-S$ -lower alkyl,  $-(CH_2)_m-S$ -lower alkenyl, or  $-(CH_2)_n-S-(CH_2)_m-R_7$ ;

$R_5$  represents a hydrogen, an alkyl, an alkenyl, an alkynyl,  $-C(X_1)(X_2)X_3$ ,  $-(CH_2)_m-R_7$ ,  $-(CH_2)_n-OH$ ,  $-(CH_2)_n-O$ -alkyl,  $-(CH_2)_n-O$ -alkenyl,  $-(CH_2)_n-O$ -alkynyl,  $-(CH_2)_n-O$ - $-(CH_2)_m-R_7$ ,  $-(CH_2)_n-SH$ ,  $-(CH_2)_n-S$ -alkyl,  $-(CH_2)_n-S$ -alkenyl,  $-(CH_2)_n-S$ -alkynyl,  $-(CH_2)_n-S-(CH_2)_m-R_7$ ,  $-C(O)C(O)NH_2$ , or  $-C(O)C(O)OR'$ ;

$R_6$  represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl,  $-(CH_2)_m-R_7$ ,  $-(CH_2)_m-OH$ ,  $-(CH_2)_m-O$ -alkyl,  $-(CH_2)_m-O$ -alkenyl,  $-(CH_2)_m-O$ -alkynyl,  $-(CH_2)_m-O-(CH_2)_m-R_7$ ,  $-(CH_2)_m-SH$ ,  $-(CH_2)_m-S$ -alkyl,  $-(CH_2)_m-S$ -alkenyl,  $-(CH_2)_m-S$ -alkynyl,  $-(CH_2)_m-S-(CH_2)_m-R_7$ ,



$R_7$  represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

$R'$  represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

$R_8$  and  $R_9$  each independently represent hydrogen, alkyl, alkenyl,  $-(CH_2)_m-R_7$ ,  $C(=O)$ -alkyl,  $C(=O)$ -alkenyl,  $C(=O)$ -alkynyl, or  $C(=O)-(CH_2)_m-R_7$ ;

or  $R_8$  and  $R_9$  taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

$R_{32}$  is a small hydrophobic group;

$R_{30}$  represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group;

R<sub>50</sub> represents O or S;

R<sub>51</sub> represents N<sub>3</sub>, SH, NH<sub>2</sub>, NO<sub>2</sub> or OR'<sub>7</sub>;

R<sub>52</sub> represents hydrogen, a lower alkyl, an amine, OR'<sub>7</sub>, or a pharmaceutically acceptable salt, or R<sub>51</sub> and R<sub>52</sub> taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

Y<sub>1</sub> and Y<sub>2</sub> can independently or together be OH or an alkoxy, or taken together Y<sub>1</sub> and Y<sub>2</sub> are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

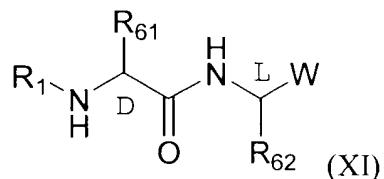
X<sub>1</sub> represents a halogen;

X<sub>2</sub> and X<sub>3</sub> each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

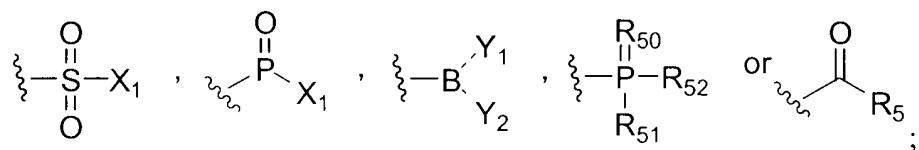
n is an integer in the range of 1 to 8.

67. (previously presented) The method of claim 38, 39, or 40, wherein the inhibitor is represented by the general Formula XI:

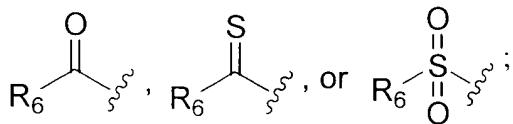


wherein,

W represents a functional group which reacts with an active site residue of the targeted protease selected from -CN, -CH=NR<sub>5</sub>,



R<sub>1</sub> represents a C-terminally linked amino acid residue or a amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group, or



R<sub>3</sub> represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-OH, -(CH<sub>2</sub>)<sub>m</sub>-O-lower alkyl, -(CH<sub>2</sub>)<sub>m</sub>-O-lower alkenyl, -(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-SH, -(CH<sub>2</sub>)<sub>m</sub>-S-lower alkyl, -(CH<sub>2</sub>)<sub>m</sub>-S-lower alkenyl, or -(CH<sub>2</sub>)<sub>n</sub>-S-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>;

R<sub>5</sub> represents H, an alkyl, an alkenyl, an alkynyl, -C(X<sub>1</sub>)(X<sub>2</sub>)X<sub>3</sub>, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>n</sub>-OH, -(CH<sub>2</sub>)<sub>n</sub>-O-alkyl, -(CH<sub>2</sub>)<sub>n</sub>-O-alkenyl, -(CH<sub>2</sub>)<sub>n</sub>-O-alkynyl, -(CH<sub>2</sub>)<sub>n</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>n</sub>-SH, -(CH<sub>2</sub>)<sub>n</sub>-S-alkyl, -(CH<sub>2</sub>)<sub>n</sub>-S-alkenyl, -(CH<sub>2</sub>)<sub>n</sub>-S-alkynyl, -(CH<sub>2</sub>)<sub>n</sub>-S-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -C(O)C(O)NH<sub>2</sub>, or -C(O)C(O)OR';

R<sub>6</sub> represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-OH, -(CH<sub>2</sub>)<sub>m</sub>-O-alkyl, -(CH<sub>2</sub>)<sub>m</sub>-O-alkenyl, -(CH<sub>2</sub>)<sub>m</sub>-O-alkynyl, -(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>, -(CH<sub>2</sub>)<sub>m</sub>-SH, -(CH<sub>2</sub>)<sub>m</sub>-S-alkyl, -(CH<sub>2</sub>)<sub>m</sub>-S-alkenyl, -(CH<sub>2</sub>)<sub>m</sub>-S-alkynyl, or -(CH<sub>2</sub>)<sub>m</sub>-S-(CH<sub>2</sub>)<sub>m</sub>-R<sub>7</sub>;

R<sub>7</sub> represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'<sub>7</sub> represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R<sub>61</sub> and R<sub>62</sub>, independently, represent small hydrophobic groups;

Y<sub>1</sub> and Y<sub>2</sub> can independently or together be OH or an alkoxy, or taken together Y<sub>1</sub> and Y<sub>2</sub> are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

R<sub>50</sub> represents O or S;

R<sub>51</sub> represents N<sub>3</sub>, SH, NH<sub>2</sub>, NO<sub>2</sub> or OR';

R<sub>52</sub> represents hydrogen, a lower alkyl, an amine, OR', or a pharmaceutically acceptable salt, or R<sub>51</sub> and R<sub>52</sub> taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X<sub>1</sub> represents a halogen;

X<sub>2</sub> and X<sub>3</sub>, independently for each occurrence, represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

68. (New) The method of any of claims 38-40, wherein the total dosage is less than 2000 mg.